IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Weers et al. Application No: 09/851,226 Confirmation No: 4017 Filed: May 8, 2001 Title: PHOSPHOLIPID-BASED POWDERS FOR DRUG DELIVERY	Group Art Unit: 1617 Examiner: HUI, San Ming Jr. Attorney Docket No: NK.73.US September 8, 2005 San Francisco, California

DECLARATION OF DR. JEFFRY G. WEERS UNDER 37 C.F.R. § 1.132

I, Jeffry G. Weers, hereby declare:

1. I am a co-inventor the instant application and I currently employed by Nektar Therapeutics Inc. in the position of Senior Director, Product Development, at NEKTAR THERAPEUTICS, INC. the assignee of the present application.

2. I have a Ph.D. in Physical Chemistry from the University of California, Davis, California, and a B.S., Honors in Chemistry, University of Puget Sound, Tacoma, Washington. I have over 20 years of experience in the research and development of colloids and the use of polymers and surfactants in drug delivery. I am an inventor in numerous patents, have publications in refereed journals, and have been an invited presentor at scientific conferences. I am currently Section Editor and on the Editorial Board of the journal Current Opinion in Colloid & Interface Science and Guest Editor for Colloids and Surfaces. I have attached hereto a copy of my curriculum vitae which demonstrates that I am an expert in the field of aerosolized medications and have particular knowledge and understanding of the formulation and processing challenges in developing phospholipid compositions of sufficient physical and chemical stability to be suitable for formulating as spray dried powders intended for administration via inhalation.

3. I have reviewed the above-identified patent application, the claims being presented by amendment, the office actions which have been entered in this case, and the references relied upon by the Examiner.

4. It is my opinion that the invention, as claimed, would not have been obvious to one of ordinary skill in the art over any combination of references cited by the Examiner and any other combination of references of which I am aware due to the unexpected benefits increasing the physical stability and dispersibility of the particles comprising saturated phospholipid and a polyvalent cation, the molar ratio of polyvalent cation to phospholipid being at least 0.05 and sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation.

5. As explained in the Specification of the present patent application, phospholipids are especially difficult to formulate as dry powders as their low gel to liquid transition temperature (Tm) values and amorphous nature lead to powders which are very sticky and difficult to deaggregate and aerosolize. The gel to liquid transition temperatures of the phospholipids are critical to obtaining phospholipids-based powders that both flow well and are readily dispersible from a dry powder device.

6. We discovered that polyvalent cations unexpectedly substantially increase the Tm of saturated phospholipids, providing numerous benefits including better storage stability of the powders, improved dispersibility, reduced likelihood of absorbing atmospheric water, better lung distribution, and improved emitted dose and fine particle fraction. The unexpected increase in Tm of saturated phospholipids such as DSPC and DDPC, when polyvalent ion is added in the molar ratios of 0.25 to 1, is shown in Tables I and II below:

<u>Table I (DSPC)</u>

Ca/DSPC (mol/mol)	Tm (°C)
0	79
0.25	85
0.5	98
1.0	126

<u>Table II (DPPC)</u>

Ca/DSPC (mol/mol)	Tm (°C)
0	63
0.25	69
0.5	89

7. It is surprising that the addition of a polyvalent ion, such as divalent calcium, would affect the Tm of the phospholipids at all. We believe that the calcium ions intercalate the phospholipids membrane to interact directly with the negatively charged portion of the

saturated headgroup of the phospholipid resulting in the dehydration of the head group and condensation of the acryl-chain packing, all of which leads to the increased thermodynamic stability of the phospholipid, as explained at page 8, lines 24-28 of the instant Specification.

8. It is further surprising that the addition of a polyvalent cation, for example, in the form of a highly hygroscopic salt such as calcium chloride, would stabilize a dry powder prone to moisture induced destabilization, as one would expect that salts such as calcium chloride would readily pick up water leading to particle aggregation. Figure 1 shows a dynamic vapor adsorption (DVS) graph that plots the change in %mass for increasing molar ratio of DSPC to calcium chloride. As the ratio of amount of calcium polyvalent ion to phospholipid was increased to a about 2:1 (which is the reverse of, but corresponds to, the claimed 0.5:1 ratio of saturated phospholipid to polyvalent cation), unexpectedly, the resultant spray dried particle had about the same moisture absorption properties. It would be expected that the addition of calcium chloride, which is hygroscopic and absorbs water from the atmosphere, would increase the moisture absorption properties of phospholipid; however, it does not do so because the polyvalent calcium ion modifies the structure of the phospholipid thereby no longer existing as hydroscopic calcium chloride.

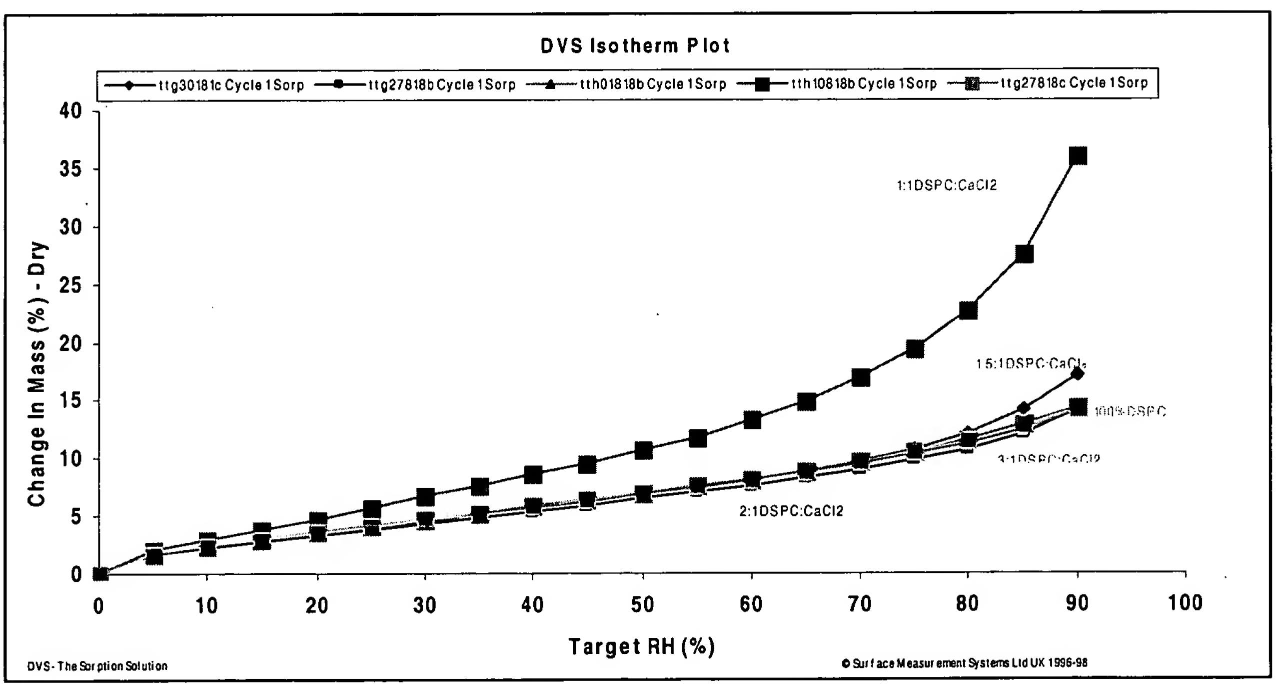

Figure 1.

9. In making the obviousness rejections, the Examiner relies heavily upon the teachings of a patent of which I am the first named inventor, U.S. patent no. 6,309,623 to Weers et al..

10. However, the Weers et al. patent does not teach particles comprising an active agent, a saturated phospholipid and a polyvalent cation, in which the molar ratio of polyvalent cation to phospholipid is at least 0.05 and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation, as claimed in claim 2 of the instant patent application.

11. Instead, in the Weers et al. patent, we teach particles having a structural matrix that comprising a surfactant such as a phospholipid which has a preselected, naturally occurring, gel to liquid crystal phase transition temperatures. We specifically teach preselecting lipids "that have a gel to liquid crystal phase transition greater than about 40°C." (Weers et al., Column 16, lines 44-49). Thus, in the Weers et al. patent, we teach the <u>selection</u> of lipid surfactants that have a particular gel to liquid transition temperature.

12. However, in the Weers et al. patent, we do not teach chemically modifying phospholipid by a polyvalent cation in a selected molar ratio to change the structure of the phospholipid to obtain a new phospholipid having a gel to liquid transition temperature that is higher than that of the unmodified phospholipid.

13. In other words, Weers et al. teaches that the problem of the excessive low Tm of phospholipids is easily solved by selecting only those phospholipids which have high gel to liquid transition temperatures above 40°C. Thus, Weers at al. would not provide any motivation to one of ordinary skill in the art to try to modify the structure of a phospholipid to obtain a higher gel to liquid transition temperature, because such modification is not taught, or is even taught as unnecessary because it is solved through selection.

14. The Examiner acknowledges that "Weers et al. lacks an exemplification of a composition comprising saturated phospholipid and divalent cation, and a teaching of the ratio of cation to phospholipid." But, further, in Weers et al. we simply do not teach or suggest the claimed solution of chemically altering a saturated phospholipid to provide an increased gel to liquid crystal phase transition temperature.

15. Nor do we teach in Weers et al. that a chemical capable of chemically modifying a saturated phospholipid to achieve a higher Tm is a polyvalent cation. Instead in Weers et al. we only mention calcium chloride, in the context of "optional components that may include conventional viscosity modifiers, buffers such as phosphate buffers or other conventional biocompatible buffers or pH adjusting agents such as acids or bases…." The calcium chloride recited in Weers et al. is only taught as an example of a suitable acidic or basic salt to modify pH etc., but not as a Tm modifier for a phospholipid.

16. Further, in Weers et al. we do not teach that a molar ratio of polyvalent cation of greater than 0.5 is needed to modify the phospholipid to achieve a higher Tm. Nor do we teach the desirability of selecting a particular molar ratio of polyvalent ion that can change the structure of the phospholipid to obtain a new structure having a gel to liquid transition temperature that is higher than that of the unmodified phospholipid. In fact, no molar ratios of cation to phospholipid are taught at all in Weers et al.

17. Furthermore, the instant claims are to a saturated phospholipid with added polyvalent ion which is not taught by the combination of Weers et al. and Materne et al.. Materne et al. describes the use of calcium chloride only in combination with unsaturated phosphatidylcholine. Although not explicitly stated in Materne, it is clear to one of ordinary skill in the art that the phosphatidylcholines described by Materne et al. are unsaturated because of their physicochemical properties and appearance. Specifically, Materne et al. teaches that the phosphatidylcholines as plastic materials of low stability, which are difficult to process and handle. This is an accurate description of unsaturated phosphatidylcholines with a Tm<10 °C, in which the particles often fuse into large agglomerates due to temperature or moisture induced aggregation. Unsaturated phosphatidylcholines are also unstable due to oxidative processes involving the double bonds and must typically be stored at -20°C to maintain stability.

18. Furthermore, Materne describes phosphatidylcholines which have a yellow color. This yellow color is typically a result of oxidative processes involving the double bond presented in unsaturated materials; further evidencing that the taught phospholipids are not saturated. The phosphatidylcholines taught by Materne et al. are intended for use in preparing phosphatidylcholines raw material and not as a final pharmaceutical product where the physical properties of the lipids are much more demanding.

19. In contrast, the claimed saturated phospholipids are flowable powders in their natural state which are stable chemically since they contain no double bonds that can be oxidized. Further, saturated phospholipids such as saturated phosphatidylcholines are not difficult to handle under normal ambient conditions. Saturated phosphatidylcholines are also typically white in appearance, not yellow.

20. For these reasons, the combination of Weers et al. and Materne et al. simply do not teach the claimed subject matter comprising particles comprising an active agent, a saturated phospholipid and a polyvalent cation, wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation, as claimed in claim 2 of the instant patent application.

21. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Jeffry G. Weers

8-Sep-05
Date

CURRICULUM VITAE

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SUMMARY

Physical chemist with a broad multidisciplinary scientific background, and 20 years of experience in colloid-based research and development. Expert in the use of polymers and surfactants in drug delivery. Extensive experience with a wide variety of colloidal drug delivery systems including: micelles, microemulsions, emulsions, liposomes, microparticles, microbubbles, foams, liquid crystals, suspensions, and aerosols. Demonstrated leadership skills in supervisory and matrix team environments. Have led many technically challenging projects that are currently in various stages of development, from preclinical to post-approval. Innovative, accomplishment oriented. Holder of numerous patents, publications in refereed journals and an invited presentor at scientific conferences. Significant experience in business development and strategic planning. Section Editor and member of the Editorial Board for the journal *Current Opinion in Colloid & Interface Science*, Guest Editor for *Colloids and Surfaces*. Positive motivator and mentor with a reputation for developing people.

EDUCATION

Ph.D., Physical Chemistry, University of California, Davis, CA (1985)
B.S., Honors in Chemistry, University of Puget Sound, Tacoma, WA. (1980)

PROFESSIONAL EXPERIENCE

NEKTAR THERAPEUTICS, San Carlos, CA (2005-present)
Senior Director, Product Development
Responsible for formulation research and development from new concepts through late stage development and NDA approval.

TRANSAVE INC., Monmouth Junction, NJ (2004-2005)
Vice President, Research and Development

Transave is focused on developing sterile controlled release formulations for inhalation based on encapsulation of therapeutics in liposomes. I was responsible for all aspects of Research and Development, managing both in-house R&D and R&D activities by outside consultants, contractors, etc. This included leadership of Product Development, Preclinical, Manufacturing and Research activities. I was a senior spokesperson for the Company internally to the Board of Directors, and to other companies, vendors, investors, and potential partners in R&D collaborations. I interacted with the Medical Officer on clinical and regulatory matters and with other Senior Executives on business development, budgets, and timelines. I was responsible for keeping the new product pipeline filled and assisting in the evaluation of new technologies.

- Directed preparation of the CMC and Preclinical Sections of the IND for liposomal cisplatin for inhalation; Phase II clinical trials are in progress in metastatic osteosarcoma
- Directed reformulation of the liposomal cisplatin drug product resulting in a five-fold reduction in nebulization time
- Directed preparation of the CMC and Preclinical Sections of the IND for liposomal amikacin; Phase II clinical trials to be conducted in te U.S. with the Therapeutic Development Network based on a grant received from the Cystic Fibrosis Foundation

- Directed reformulation of the liposomal amikacin drug product resulting in a three-fold reduction in administration time

NEKTAR THERAPEUTICS (formerly Inhale Therapeutic Systems), San Carlos, CA (1999-2004)
Director, Advanced Particle Research, Technical Leader, PulmoSphere® Technology, Director, R&D Administration, Senior Nektar Fellow, Scientific Research

Joined Inhale as part of the acquisition of the *PulmoSphere* technology. Led integration of technology into Inhale's core business. The *PulmoSphere* platform allowed Inhale to enter the small molecule delivery space with a superior powder technology, delivered from a simple, portable, passive dry powder inhaler (DPI). Doses as high as 66 mg can be delivered from the DPI in a single breath, opening opportunities for delivering therapeutics previously not possible in DPIs. The *PulmoSphere* technology has multiple partnered and proprietary products currently in clinical development. Role expanded into corporate planning across all three Nektar business units. Co-led the development of Nektar's short-term and long-term technology strategies. Included was an assessment of Nektar's core technologies in inhalation (San Carlos), advanced PEGylation (Huntsville), and supercritical fluid processing (Bradford, UK). Work included assessments of third party drug delivery technologies in the oral, parenteral, and inhalation spaces.

- Directed formulation development, process development, and clinical manufacturing of four Phase I clinical studies involving the PulmoSphere platform.
  - Demonstrated that ≈70% of the emitted budesonide dose could be delivered to patient's lungs from a passive dry powder inhaler independent of their peak inspiratory effort. The best commercial DPIs currently deliver no more than 30% to patient's lungs with dramatic flow rate dependence
  - Demonstrated clinically that 25 mg of tobramycin powder for inhalation could be delivered from a passive DPI in a single breath. This opened the door for delivery of antiinfectives and other less potent drugs with a portable inhaler, thereby decreasing administration times relative to nebulization, and likely improving patient compliance
- Led formulation and process development of tobramycin powder for inhalation (TPI); product was partnered with Chiron and is scheduled to initiate Phase III clinical testing in 2005
- Developed the regulatory strategy and supply chain for blowing agents in PulmoSphere products
- Developed formulation strategy for insoluble lipophilic drugs with low Tg based on dispersion of nanoparticles in the *PulmoSphere* matrix
- Demonstrated the importance of particle density in improving fluidization and dispersibility in small porous particles
- Demonstrated that peptides (e.g., insulin, leuprolide, parathyroid hormone, follicle stimulating hormone), proteins (e.g., hGH, hIgG), and viruses (e.g., influenza virus) can be formulated as dry powders in the PulmoSphere matrix.
- Technical lead on several external technology evaluations and diligence efforts for potential drug delivery company acquisitions
- Aided Marketing in the development of the Business Development pulmonary platform presentation; provided guidance on web page design; participated in external marketing interviews regarding Nektar technology (e.g., interview on Bio.com).
- Technical lead on business development trips that resulted in the signing of multiple feasibility agreements and development deals with Chiron and Johnson & Johnson.
- Proficient in the stabilization of macromolecules in dry powders comprised of amorphous glasses

ALLIANCE PHARMACEUTICAL CORP., San Diego, CA (1991-1999)
Manager/Director/Senior Director of Exploratory Pharmaceutical Research

Successfully led the pharmaceutical research group for a start-up biotechnology company. Directed research efforts towards the development of engineered particles for biomedical applications.

- Designed lipid-based microparticles for mucosal vaccination in conjunction with A. Bot
- Lead inventor of novel metered dose inhaler and dry powder inhaler formulations based on engineered particles designed to be both hollow and porous.
    - Led early pharmaceutical and business development of Alliance's *PulmoSphere®* drug delivery program (licensed to Inhale for ≈$25M + royalties)
- Co-inventor of several patents related to the delivery of drugs in perfluorocarbon continuous phases.
- Co-inventor of poloxamer-based thermoreversible gels for post-surgical adhesion prevention, parenteral drug delivery, and gastric retentive drug delivery systems. Patents focused on control of gelation temperature by the inclusion of fatty acid soaps, and dissolution time and mechanism (erosion control vs. diffusion control) with polymeric mixtures.
- Led successful formulation effort to eliminate complement activation in early parenteral ultrasound formulations.
- Co-inventor of gas emulsion (microbubble) formulation used as a contrast agent for diagnostic ultrasound procedures; the technology was licensed to Schering AG for $65M plus royalties; approved in Jun-2002 by FDA for endocardial border delineation. Imagent acquired by Photogen Technologies
- Co-inventor of partial liquid ventilation (PLV). PLV completed pivotal Phase III trials. No statistical significance was observed over conventional mechanical ventilation in the treatment of ARDS/ALI patients. LiquiVent was originally partnered with Aventis.
- Directed molecular modeling/QSPR studies leading to group contribution methods for determining the boiling point, refractive index, and lipophilicity of fluorinated materials
- Directed development of theory relating droplet coalescence to the spontaneous curvature of nucleation holes in liquid films separating droplets
- Led basic research program aimed at understanding the mechanisms of perfluorocarbon emulsion coarsening (i.e. Ostwald ripening, coalescence).
- Lead inventor of the *Oxygent*™ (parenteral fluorocarbon-in-water emulsion) formulation currently in Phase III clinical trials. In the process solved the emulsion stability/organ retention dilemma that had plagued formulators in this field. Over the years Oxygent has been partnered with: Boehringer Ingelheim, Johnson & Johnson, and Baxter.
- Headed a company-wide reformulation effort designed to eliminate biological side-effects observed in parenteral perfluorocarbon emulsion ("blood substitute") formulations. Efforts resulted in clinically significant improvements in febrile and thrombocytopenia responses relative to earlier formulations.
- Contributed to the development and regulatory approval of Imagent® GI, Imagent® US, and SatPad®.

THE CLOROX COMPANY, Pleasanton, CA (1985-1990)
Scientist II, Senior Scientist

Initiated new projects involving mixed surfactant systems including the following:

- Developed thickened bleach solutions with worm-like cationic micelles. Investigations led to the development of *"Industrial Strength Liquid Plumr.*
- Developed a solvent-free ("green") cleaning technology based on mixed surfactants that was as effective as Formula 409.
- Developed a spherulitic (multilamellar vesicle) aqueous delivery system for lipase enzymes.
- Light scattering studies conducted in Professor Kaler's lab (U Washington) spawned discovery of spontaneous vesicle formation in anionic/cationic surfactant mixtures
- Characterized solubilization of polar and nonpolar solutes in mixed micelles
- Characterized micellar sphere to rod transitions in mixed surfactant systems via Fourier transform infrared spectroscopy, quasielastic light scattering, dynamic rheology, and tensiometry.

UNIVERSITY OF CALIFORNIA, Davis, CA (1981-1985)
Teaching Asst., Research Asst.

Thesis research involved examination of electronic energy transfer in organic and biological systems.

- Provided the first measurement of spin sublevel kinetics in triplet-singlet energy transfer processes.
- Showed that the spin sublevel selectivity in triplet-triplet energy transfer requires time for precession about the spin axis (a statement of the Heisenberg uncertainty principle).
- Examined energy transfer between tryptophan and heme groups in modified hemoglobins (pertinent to patients suffering from lead intoxication and erythropoietic protoporphyria).
- Examined spin lattice relaxation of naphthalene in a Shpol'skii matrix at 1.2 to 2.4 °K in zero field

PROFESSIONAL AFFILIATIONS

American Chemical Society
American Association of Pharmaceutical Scientists
International Society for Aerosols in Medicine
Controlled Release Society
Guest Editor for Colloids Surfaces A: Physicochemical and Engineering Aspects
Section Editor and member of the Editorial Board for Current Opinion in Colloid & Interface Science

PUBLICATIONS

58. Weers JG, Metzheiser B, Perkins W, Meers P, Nicholson S, Taylor G, Warren S, Kanter P, Saiman L, Pilkiewicz F: **A gamma scintigraphy study to investigate lung deposition and clearance of inhaled amikacin-loaded liposomes (SLIT™ Amikacin) in healthy male volunteers.** *Pharm Res,* in preparation.

57. Patton JS, Fishburn CS, Weers JG: **The lungs as a portal of entry for systemic drug delivery.** *Proc Am Thor Soc* 2004, **1**:338-344.

56. Tarara TE, Hartman M, Gill H, Kennedy A, Weers JG: **Characterization of suspension-based metered dose inhaler formulations comprised of spray-dried budesonide crystals dispersed in HFA-134a.** *Pharm Res* 2004, **21**:1607-1614.

55. Weers JG, Arlauskas RA, Tarara TE, Pelura TJ: **Characterization of fluorocarbon-in-water emulsions with added triglyceride.** *Langmuir* 2004, **20**:7430-7435.

54. Weers JG, Arlauskas RA: **Particle size analysis of perfluorocarbon emulsions in a complex whole blood matrix by sedimentation field-flow fractionation.** *Colloids Surf B* 2004, **33**:265-269.

53. Newhouse MT, Hirst PH, Duddu SP, Walter YH, Tarara TE, Clark AR, Weers JG: **Efficient and reproducible pulmonary delivery of tobramycin using an engineered PulmoSphere powder.** *Chest* 2003, **124**:360-366.

52. Duddu SP, Sisk SA, Walter YH, Tarara TE, Trimble K, Clark AR, Eldon M, Elton RC, Pickford M, Hirst PH, Newman SP, Weers JG: **Improved lung delivery from a passive dry powder inhaler using an engineered PulmoSphere powder.** *Pharm Res* 2002, **19**:689-695.

51. Hirst PH, Elton RC, Pitcairn GR, Newman SP, Weers JG, Clark AR, Tarara TE, Dellamary LA, Hall G, Shorr J: **In vivo lung deposition of hollow porous particles from a pressurized metered dose inhaler.** *Pharm Res* 2002, **19**:258-264.

50. Dickson EW, Heard SO, Tarara TE, Weers JG, Brueggemann BA, Doern GV: **Liquid ventilation with perflubron in the treatment of rats with pneumococcal pneumonia.** *Crit Care Med* 2002, **30**:393-395.

49. Venthoye G, Weers J, Tarara T: **PulmoSphere particle engineering technology development to pilot scale and commercial viability.** *Proc Drug Delivery to the Lungs XII,* London 2001, p 50-52.

48. Smith DJ, Gambone LM, Tarara T, Meays DR, Dellamary LA, Woods CM, Weers J: **Liquid dose pulmonary instillation of gentamicin PulmoSpheres formulations: tissue distribution and pharmacokinetics in rabbits.** *Pharm Res* 2001, **18**:1556-1561.

47. Sisk SA, Newhouse MT, Duddu SP, Walter Y, Eldon M, Tarara T, Clark AR, Weers J: **Intrasubject reproducibility and high efficiency of large dose tobramycin from a dry powder inhaler in healthy volunteers.** *J Aerosol Med* 2001, **14**:392 (abstract).

46. Bot AI, Smith DJ, Bot S, Dellamary L, Tarara TE, Phillips W, Weers JG, Woods, CM: **Receptor-mediated targeting of spray-dried lipid particles co-formulated with immunoglobulin and loaded with a prototype vaccine.** *Pharm Res* 2001, **18**:971-979.

45. Tzannis S, Weers J: **Dan Lasic (1952-2000): Pioneer in the development of liposomes in medicine.** *Curr Opin Colloid Interface Sci* 2001, **6**:91-92.

44. Weers JG: **Dispersible powders for inhalation applications.** *Innov Pharm Tech* 2000, **1(7)**:111-116.

43. Bot AI, Tarara TE, Smith DJ, Bot SR, Woods CM, Weers JG: **Novel lipid-based hollow-porous microparticles as a platform for immunoglobulin delivery to the respiratory tract.** *Pharm Res* 2000, **17**: 274-282.

42. Dellamary LA, Tarara TE, Smith DJ, Woelk CH, Adractas A, Costello M, Gill H, Weers JG: **Hollow porous particles in metered dose inhalers.** *Pharm Res* 2000, **17**:168-174.

41. Kabalnov A, Klein D, Pelura T, Schutt E, Weers J: **Dissolution of multicomponent microbubbles in the bloodstream 1. theory.** *Ultrasound Med Biol* 1998, **24**:739-749.

40. Kabalnov, A, Bradley J, Flaim S, Klein D, Pelura T, Peters B, Otto S, Reynolds J, Schutt E, Weers J: **Dissolution of multicomponent microbubbles in the bloodstream 2. experiment.** *Ultrasound Med Biol* 1998, **24**:751-760.

39. Weers JG: **Colloidal particles in drug delivery.** *Curr Opin Colloid Interface Sci* 1998, **3**:540-544.

38. Faithfull NS, Weers JG: **Perfluorocarbon compounds.** *Vox Sang* 1998, **74**:243-248.

37. Weers JG, Jones MN: **Editorial overview; biosurfaces revisited.** *Curr Opin Colloid Interface Sci* 1997, **2**: 501-502.

36. Kabalnov AS, Weers JG, Tarara TE, Arlauskas RA: **Phospholipids as emulsion stabilizers 2. phase behavior versus emulsion stability**. *J Colloid Interface Sci* 1996, **184**:227-235.

35. Jones MN, Weers JG: **Editoral overview; biosurfaces: new problems, new solutions**. *Curr Opin Colloid Interface Sci* 1996, **1**:635-637.

34. Riess JG, Weers JG: **Emulsions for biomedical uses.** *Curr Opin Colloid Interface Sci* 1996, 1:652-659.

33. Kabalnov AS, Weers JG: **Kinetics of mass transfer in micellar solutions: surfactant adsorption, solubilization kinetics, and ripening**. *Langmuir* 1996, **12**:3442-3448.

32. Kabalnov AS, Weers JG: **Macroemulsion stability within the Winsor III region: theory vs. experiment**. *Langmuir* 1996, **12:**1931-1935.

31. Arlauskas RA, Weers JG: **Sedimentation field-flow fractionation studies of composition ripening in emulsion mixtures.** *Langmuir* 1996, **12:**1923-1925.

30. Le T, Arlauskas RA, Weers JG: **Lipophilicity characterization of fluorochemicals containing halogens or hydrocarbon blocks.** *J Fluorine Chem* 1996, **78**:155-163.

29. Smith D, Obraztsov V, Neslund G, Arlauskas R, Weers J: **Influence of particle size distribution of perflubron-based emulsions on tumor necrosis factor (TNF) release from rat monocytes in-vitro.** *Art Cells Blood Sub Immob Biotech* 1996, **24**:432 (abstract).

28. Weers JG, Harris MB, Otto S, Arlauskas RA: **The use of lipophilic secondary fluorocarbons to solve the emulsion stability/organ retention dilemma in blood substitutes**. *Art Cells Blood Sub Immob Biotech* 1996, **24**:458 (abstract).

27. Kabalnov AS, Weers JG, Arlauskas RA, Tarara TE: **Phospholipids as emulsion stabilizers. 1. interfacial tensions.** *Langmuir* 1995, **11**:2966-2974.

26. Weers JG, Arlauskas RA: **Sedimentation field-flow fractionation studies of Ostwald ripening in fluorocarbon emulsions containing two disperse phase components.** *Langmuir* 1995, **11**:474-477.

25. Riess JG, Flaim SF, Klein DH, and Weers JG**: The relative physicochemical and biological attributes of perflubron emulsions.** *Proc Int Symp Blood Substitutes*, 1994 (Vorobyev SI, Ivanitsky GR, Eds) Russian Academy of Sciences, Pushchino, Russia, 1995.

24. Le T, Weers JG: **Group contribution-additivity and quantum mechanical models for predicting the molar refractions, indices of refraction, and boiling points of fluorocarbons.** *J Phys Chem* 1995, **99:**13909-13916.

23. Le T, Weers JG: **QSPR and GCA models for predicting the normal boiling point of fluorocarbons.** *J Phys Chem* 1995, **99:**6739-6747.

22. Flores-Aguilar M, Weers JG et al**: Intraocular tolerance of perfluorooctylbromide (perflubron).** *Retina* 1995, **15:**3-13.

21. Postel M, Riess JG, Weers JG: **Fluorocarbon emulsions - the stability issue**. *Art Cells Blood Sub & Immob Biotech* 1994, **22:**991-1005.

20. Arlauskas RA, Klein DH, Weers JG: **Analysis of Ostwald ripening in fluorocarbon emulsions by sedimentation field-flow fractionation.** *Art Cells Blood Sub Immob Biotech* 1994, **22:**1317-1323.

19. Weers JG, Ni Y, Tarara TE, Pelura TJ, Arlauskas RA. **The effect of molecular diffusion on initial particle size distributions in phospholipid-stabilized fluorocarbon emulsions**. *Colloids Surfaces A: Physicochem Eng Aspects* 1994, **84:**81-87.

18. Schutt E, Barber P, Fields T, Flaim S, Horodniak J, Keipert P, Kinner R, Kornbrust L, Leakakos T, Pelura T, and Weers J: **Proposed mechanism of pulmonary gas trapping (PGT) following intravenous perfluorocarbon emulsion administration.** *Art Cells Blood Sub Immob Biotech* 1994, **22:**1205-1214.

17. Weers JG, Liu J, Fields T, Resch P, Cavin J, Arlauskas RA: **Room temperature stable perfluorocarbon emulsions with acceptable half-lives in the reticuloendothelial system.** *Art Cells Blood Sub Immob Biotech* 1994, **22:**1175-1182.

16. Keipert PE, Otto S, Flaim SF, Weers JG, Schutt EA, Pelura TJ, Klein DH, Yaksh TL: **Influence of perflubron emulsion particle size on blood half-life and febrile response in rats.** *Art Cells Blood Sub Immob Biotech* 1994, **22:**1169-1174.

15. Klein DH, Jones RC, Keipert PE, Luena GA, Otto S, Weers JG: **Intravascular behavior of perflubron emulsions.** *Colloids Surfaces A: Physicochem Eng Aspects* 1994, **84:**89-95.

14. Riess JG, Weers JG: **Preface to special issue: colloid and surface chemistry of fluorocarbons and highly fluorinated amphiphiles.** *Colloids Surfaces A: Physicochem Eng Aspects* 1994, **84:**vii.

13. Weers JG, Riess JG: **Colloid and surface chemistry of fluorocarbons and highly fluorinated amphiphiles.** *PRF Annual Report* 1993, **37:**542.

12. Weers JG: **A physicochemical evaluation of perfluorochemicals for oxygen transport applications.** *J Fluorine Chem* 1993, **64:**73-93.

11. Pelura TJ, Johnson CS, Tarara TE, Weers JG**: Stabilization of perflubron emulsions with egg yolk phospholipid.** *Biomat Artif Cell and Immob Biotech* 1992, **20:**845-848; In: *Blood Substitutes and Oxygen Carriers* (Chang TMS, Ed.) Marcel Dekker Inc, 1993, p 615.

10. Weers JG, Scheuing DR: **Structure/performance relationships in monoalkyl/dialkyl cationic surfactant mixtures.** *J Colloid Interface Sci* 1991, **145:**563-580.

9. Weers JG *et al*: **Effect of the intramolecular charge separation distance on the solution properties of betaines and sulfobetaines**. *Langmuir* 1991, **7:**854-867.

8. Weers JG, Reboa PF, Scheuing DR: **Characterization of viscoelastic surfactant mixtures II: rheological studies.** *Colloids Surfaces* 1991, **55:**57-72.

7. Scheuing DR, Weers JG: **Characterization of viscoelastic surfactant mixtures I: Fourier transform infrared spectroscopic studies.** *Colloids Surfaces* 1991, **55:**41-56.

6. Weers JG, Rathman JF, Scheuing DR. **Structure/performance relationships in long-chain dimethylamine oxide/sodium dodecylsulfate surfactant mixtures.** *Colloid Polym Sci* 1990, **268:**832-846.

5. Weers JG: **Solubilization in mixed micelles.** *J Amer Oil Chem Soc* 1990, **67:**340-345.

4. Scheuing DR, Weers JG: **A Fourier transform infrared spectroscopic study of dodecyltrimethylammonium chloride/sodium dodecylsulfate surfactant mixtures.** *Langmuir* 1990, **6:**665-671.

3. Weers JG, Maki AH: **Optically detected magnetic resonance studies of electronic energy transfer in the complex of auramine O with horse liver alcohol dehydrogenase.** *Biochemistry* 1986, **25:**2897-2904.

2. Ghosh S, Weers JG, Petrin M, Maki AH: **Anisotropic spin-lattice relaxation in the triplet state of naphthalene in n-pentane.** *Chem Phys Letters* 1984, **108:**87-93.

1. Maki AH, Weers JG, Hilinski EF, Milton SV, Rentzepis PM: **Time-resolved spectroscopy of intramolecular energy transfer in a rigid spiran.** *J Chem Phys* 1984, **80:**2288-2297.

BOOK CHAPTERS

9. Weers J, Clark A, Challoner P: **High dose inhaled powder delivery: challenges and techniques.** In: *"Respiratory Drug Delivery IX"*, (Dalby RN, Byron PR, Peart J, Suman JD, and Farr SJ, Eds), Amy Davis Biggs, River Grove, IL, 2004, p. 281-288.

8. Bot A, Smith D, Tarara T, Harders S, Bot S, Langsetmo I, Woods C, Weers J: **Vaccination by antigen delivery to airway antigen presenting cells via engineered, lipid-based microparticles.** In: *"Respiratory Drug Delivery VII"*, (Dalby RN, Byron PR, Farr SJ, Eds), Interpharm Press Inc, Buffalo Grove, IL, 2000, p. 327-328.

7. Tarara TE, Weers JG, Dellamary LA: **Engineered powders for inhalation.** In: *"Respiratory Drug Delivery VII"*, (Dalby RN, Byron PR, Farr SJ, Eds), Interpharm Press Inc, Buffalo Grove, IL, 2000, p. 413-416.

6. Weers JG, Tarara TE, Gill H, English BS, Dellamary LA: **Homodispersion technology for HFA suspensions: particle engineering to reduce dosing variance.** In: *"Respiratory Drug Delivery VII"*, (Dalby RN, Byron PR, Farr SJ, Eds), Interpharm Press Inc, Buffalo Grove, IL, 2000, p. 91-97.

5. Krafft MP, Riess JG, Weers JG: **The design and engineering of oxygen-delivering fluorocarbon emulsions.** In: *Submicron Emulsions in Drug Targeting and Delivery* (Benita S, Ed) Harwood Academic Publishers, Amsterdam, 1998, p. 235-333.

4. Weers JG: **Molecular diffusion in emulsions and emulsion mixtures.** In: *Modern Aspects of Emulsion Science* (Binks BP, Ed) Royal Society of Chemistry, Cambridge, 1998, p. 292-327.

3. Weers JG, Scheuing DR: **Micellar sphere to rod transitions**. In: *FT-IR Spectroscopy in Colloid Science* (Scheuing DR, Ed) ACS Symposium Series 1991, **447:**87-122.

2. Pelura TJ, Johnson CS, Tarara TE, Weers JG: **Stabilization of perflubron emulsions with egg yolk phospholipid.** *Biomat Artif Cell and Immob Biotech* 1992, **20:**845-848; In: *Blood Substitutes and Oxygen Carriers* (Chang TMS, Ed.) Marcel Dekker Inc, 1993, p 615.

1. Weers JG: **Optically detected magnetic resonance studies of electronic energy transfer.** *Ph.D. Dissertation*, University of California, 1985.

UNITED STATES PATENTS

54. Weers JG, Tarara TE, Clark A: **Phospholipid-based powders for inhalation.** US Patent Appl No 2004/0105820 A1, published 3 Jun 04.

53. Weers J, Tarara T: **Lipid formulations for spontaneous drug encapsulation including treatment for inhalation anthrax infection and for other disorders.** US Serial No 60/xxx,xxx, filed 04 Nov 03.

52. Weers J, Tarara T: **Lipid formulations for spontaneous drug encapsulation.** US Serial No 60/xxx,xxx, filed 04 Nov 03.

51. Tarara T, Weers J: **Pharmaceutical formulation with an insoluble active agent.** US Patent Appl No 2004/0156792 A1, published 12 Aug 04.

50. Weers J, Tarara T, Eldon M, Narasimhan R: **Aerosolizable pharmaceutical formulation for fungal delivery.** US Serial No 60/437,363, filed 31 Dec 02; converted 31 Dec 03; US Patent Appl No 2004/0176391, published 9 Sep 04.

49. Weers J, Tarara T, Venthoye G: **Pulmonary delivery of aminoglycosides.** US Serial No 60/342,827, filed 19 Dec 01.

48. Kabalnov AS, Schutt EG, Weers JG: **Gas emulsions stabilized with fluorinated ethers having low Ostwald coefficients.** US Patent Appl No 20030138380 A1, published 24 Jul 03.

47. Tarara TE, Weers JG, Kabalnov A, Schutt EG, Dellamary LA: **Engineered particles and methods of use.** US Patent Appl No 2003/0064029 A1, published 3 Apr 03.

46. Flore SG, Dellamary LA, Reeve LE, Weers JG: **Methods and compositions for the delivery of pharmaceutical agents and/or the prevention of adhesions.** US Patent Appl No 2003/0108610 A1, published 12 Jun 03.

45. Gordon M, Weers J, Tarara T: **Inhalation lung surfactant therapy.** US Patent Appl No 20030099601 A1, published 29 May 03.

44. Faithfull NS, Weers JG: **Partial liquid breathing of fluorocarbons.** US Patent Appl No 2003/0056788 A1, published 27 Mar 03.

43. Weers J, Tarara TE: **Methods for administering leuprolide by inhalation.** US Patent Appl No 2003/0003057 A1, published 2 Jan 03.

42. Weers J, Tarara T: **Methods of tobramycin inhalation.** US Patent Appl No 2002/0187106 A1, published 12 Dec 02.

41. Dellamary LA, Tarara TE, Kabalnov A, Weers JG, Schutt EG: **Stabilized bioactive preparations and methods of use.** US Patent Appl No 2002/0188281 A1, published 12 Dec 02.

40. Kabalnov A, Schutt E, Weers JG: **Gas emulsions stabilized with fluorinated ethers having low Ostwald coefficients.** US Patent Appl No 2002/0119102 A1, published 29 Aug 02.

39. Schutt EG, Evitts DP, Kinner RA, Anderson CD, Weers JG: **Mixed gas microbubble compositions.** US Patent Appl No 2002/0098151 A1, published 25 Jul 02.

38. Weers JG, Klein DH, Johnson CS: **Patient oxygenation using stabilized fluorocarbon emulsions.** US Patent Appl No 2002/0065326 A1, published 30 May 02.

37. Schutt EG, Evitts DP, Kinner RA, Anderson CD, Weers JG: **Stabilized microbubble compositions.** US Patent Appl No 2002/0054854 A1, published 9 May 02.

36. Flore SG, Dellamary LA, Reeve LE, Weers JG: **Methods and compositions for the delivery of pharmaceutical agents and/or the prevention of adhesions.** US Patent Appl No 2002/0048602 A1, published 25 Apr 02.

35. Weers JG, Tarara TE, Dellamary LA, Riess JG, Schutt SG: **Phospholipid-based powders for drug delivery.** US Patent Appl No 2002/0037316 A1, published 28 Mar 02.

34. Weers JG, Tarara TE, Clark A: **Phospholipid-based powders for inhalation.** US Patent Appl No 2002/0017295 A1, published 14 Feb 02.

33. Schuler C, Nantel N, Tarara T, Weers J: **Lockout mechanism for aerosol drug delivery.** US Patent Appl No 2002/0000225 A1, published 3 Jan 02.

32. Dellamary LA, Riess J, Schutt EG, Weers JG, Tarara TE: **Stable metal ion-lipid powdered pharmaceutical compositions for drug delivery and methods of use.** US Serial No 09/568,818, filed 10 May 00; published as WO 01/85137 A2.

31. Bot A, Tarara TE, Weers JG, Kabalnov AS, Schutt EA, Dellamary LA: **Particulate delivery systems and methods of use.** US Serial No 09/720,536, filed 22 Dec 00; published as WO 00/00215.

30. Kharitonov V, Trevino L, Ranney H, Flore S, Weers J, Dellamary L, Reeve L: **Methods for delivering pharmaceutical agents to mucosal surfaces.** Published 1 Jul 99 as World Patent Application No. WO 99/32152.

29. Weers JG, Schutt EG, Dellamary LA, Tarara TE, Kabalnov AS: **Stabilized preparations for use in metered dose inhalers.** US Serial No 09/218,212, filled 22 Dec 98; published as WO 99/16422; US Patent Appl No 2004/0170568, published 2 Sep 04.

28. Dellamary LA, Kabalnov AS, Schutt EG, Tarara TE, Weers JG: **Stabilized bioactive preparations and methods of use.** US Serial No 09/218,209, filed 22 Dec 98; published as WO 99/16421.

27. Schutt EG, Tarara TE, Dellamary LA, Kabalnov AS, Weers JG: **Stabilized preparations for use in nebulizers.** US Serial No 09/218,213, filed 22 Dec 98; published as WO 99/16420.

26. Tarara TE, Weers JG, Dellamary LA, Kabalnov AS, Schutt EG: **Perforated microparticles and methods of use.** US Serial No 09/219,736, filed 22 Dec 98; published as WO 99/16419.

25. Schutt EG, Evitts DP, Kinner RA, Anderson CD, Weers JG: **Osmotically stabilized microbubble compositions.** US Patent No 6,706,253, issued 16 Mar 04.

24. Weers JG, Schutt EG, Dellamary LA, Tarara TE, Kabalnov A: **Stabilized preparation for use in metered dose inhalers.** US Patent No 6,638,495, issued 28 Oct 03.

23. Bot A, Tarara TE, Weers JG, Kabalnov AS, Schutt EA, Dellamary LA: **Particulate delivery systems and methods of use.** US Patent No. 6,630,169, issued 7 Oct 03.

22. Tarara TE, Weers JG, Kabalnov AS, Schutt EG, Dellamary LA: **Methods of spray-drying pharmaceutical compositions.** US Patent No. 6,565,885, issued 20 May 03.

21. Dellamary LA, Tarara TE, Kabalnov A, Weers JG, Schutt EG: **Stabilized bioactive preparations and methods of use.** US Patent No. 6,433,040, issued 13 Aug 02.

20. Schutt EG, Evitts DP, Kinner RA, Anderson CD, Weers JG: **Mixed gas microbubble compositions.** U.S. Patent No. 6,372,195, issued 16 Apr 02.

19. Weers JG, Schutt EG, Dellamary LA, Tarara TE, Kabalnov AS: **Stabilized preparations for use in metered dose inhalers.** U.S. Patent No. 6,309,623, issued 30 Oct 01.

18. Faithfull NS, Weers JG: **Partial liquid breathing of fluorocarbons.** U.S. Patent No. 6,289,892, issued 18 Sep 01.

17. Flore S, Dellamary L, Reeve L, Weers, JG: **Methods and compositions for the delivery of pharmaceutical agents and/or the prevention of adhesion.** U.S. Patent No. 6,280,745, issued 28 Aug 01.

16. Trevino LA, Schutt EG, Klein DH, Tarara TE, Weers JG, Kabalnov A: **Kits and systems for ultrasonic imaging.** U.S. Patent No. 6,280,705, issued 28 Aug 01.

15. Schutt EG, Evitts DP, Kinner RA, Anderson CD, Weers JG: **Osmotically stabilized microbubble preparations.** U.S. Patent No. 6,258,339, issued 10 Jul 01

14. Weers JG, Klein DH, Johnson CS: **Patient oxygenation using stabilized fluorocarbon emulsions.** U.S. Patent No. 6,204,296 issued 20 Mar 01.

13. Kabalnov A, Schutt E, Weers JG: **Stabilized gas emulsions containing phospholipids for ultrasound contrast enhancement.** U.S. Patent No. 6,193,952 issued 27 Feb 01.

12. Faithfull NS, Weers JG: **Partial liquid breathing of fluorocarbons.** U.S. Patent No. 6,119,687 issued 19 Sep 00.

11. Weers JG, Johnson C, Klein D: **Methods for the use of stabilization of fluorocarbon emulsions.** U.S. Patent No. 5,914,352 issued 22 Jun 99.

10. Weers JG, Dellamary L, Tarara TE, Trevino LA, Ranney H: **Fluorochemical solutions for the delivery of lipophilic pharmaceutical agents.** U.S. Patent No. 5,874,481, issued 23 Feb 99.

9. Faithfull NS, Weers JG: **Treatment and diagnosis of respiratory disorders using fluorocarbon liquids.** U.S. Patent No. 5,853,003, issued 29 Dec 1998.

8. Kabalnov AS, Weers JG, Schutt EG: **Gas emulsions stabilized with fluorinated ethers having low Ostwald coefficients.** U.S. Patent No. 5,804,162, issued 8 Sep 98.

7. Trevino LA, Schutt EG, Klein DH, Tarara TE, Weers JG, Kabalnov AS: **Stabilized gas emulsion containing phospholipid for ultrasound contrast enhancement.** U.S. Patent No. 5,798,091, issued 25 Aug 98.

6. Trevino LA, Dellamary L, Tarara TE, Weers JG, Ranney H: **Continuous fluorochemical microdispersions for the delivery of lipophilic pharmaceutical agents.** U.S. Patent No. 5,667,809, issued 16 Sep 97.

5. Faithfull NS, Weers JG: **Partial liquid breathing of fluorocarbons.** U.S. Patent No. 5,655,521, issued 12 Aug 97.

4. Schutt EG, Evitts DP, Kinner RA, Anderson CD, Weers JG: **Stabilized microbubble compositions.** U.S. Patent No. 5,639,443 issued 17 Jun 97.

3. Weers JG, Schutt EG, Pelura TJ, Keipert PE: **Fluorocarbon emulsions exhibiting reduced pulmonary gas trapping.** U.S. Patent No. 5,635,538 issued 3 Jun 97.

2. Weers JG, Johnson C, Klein D: **Stabilization of fluorocarbon emulsions.** U.S. Patent No. 5,628,930 issued 13 May 97.

1. Faithfull NS, Weers JG: **Partial liquid breathing of fluorocarbons.** U.S. Patent No. 5,490,498 issued 13 Feb 96.

INVITED LECTURES : 2000-2005

Engineering of powders for inhalation. Lovelace Respiratory Research Institute Annual Symposium, Albuquerque, Sept, 2005.

Pulmonary sustained release formulation of amikacin (SLIT™ Amikacin) for Pseudomonas aeruginosa infections in CF patients. American Thoracic Society International Conference, San Diego, May 2005.

Potential of liposomes in aqueous droplet inhalers. Management Forum Conference on Aqueous Droplet Inhalers, London, Oct, 2004.

High dose inhaled delivery – challenges and techniques. Respiratory Drug Delivery IX: Desert Springs, CA, Apr, 2004.

Vaccine delivery leveraging Nektar's platform technologies for inhalation. World Health Organization Meeting on Measles Vaccines, Washington DC, Feb, 2004.

Delivery of biodefense therapeutics via inhalation. Crossing Boundaries: Medical Biodefense & Civilian Medicine, Arlington, VA, Nov 2003.

The delivery of high doses via the inhalation route: a highlight of technologies and challenges. Workshop on Delivering High Doses via Inhalation: AstraZeneca, Charnwood, UK, June, 2003 (plenary).

PulmoSphere powders for inhalation. AAPS Inhalation Technology Focus Group Meeting: San Carlos, CA, September, 2002.

Hollow porous particles for inhalation therapy. Particles 2002, Orlando, FL, April 2002 (plenary).

Properties of dry powder aerosol particles. Workshop on Pulmonary Delivery and Disposition of Inhaled Aerosols, San Diego, CA, June, 2001.

Enhanced aerosol deposition using PulmoSphere technology. Australian and New Zealand Society for Respiratory Science Meeting, Sydney, Australia, 2001.

Devices for airy particulates. Management Forum Symposium on Portable Inhalers, London, UK, 7 Dec 2000.

Homodispersion technology for HFA suspensions: particle engineering to reduce dosing variance. Respiratory Drug Delivery VII, Hilton Head, SC, 2000.

Improved delivery of albuterol from pressurized metered dose inhalers using PulmoSphere technology. AAPS Annual Meeting, New Orleans, LA, 2000.

Specific Project Summaries

Project: *Oxygent Reformulation*

Situation: ALLP had recently completed Phase I clinical trials with their synthetic oxygen carrier, Oxygent™. A significant drop in platelets and large febrile response were observed. At the same time a paper was published suggesting that infusion of ALLP's drug substance, PFOB, led to hyperinflated lungs, a condition that caused death in some laboratory animals.
Action Plan: I was asked to co-lead with the Head of Pharmacology a company-wide effort aimed at: (a) identifying the root cause of the observed side-effects; (b) identifying formulation solution(s) to the problems.
Results: It was hypothesized that the drop in platelets and febrile response were the result of particulate clearance by macrophages. This process is critically dependent on the particle size distribution of the emulsion droplets. Maintaining the size of the particles below a threshold on storage is critical in maintaining biocompatibility of the emulsion. Droplet growth in these emulsions was shown to occur by molecular diffusion (Ostwald ripening). Ripening could be reduced by decreasing the water solubility of the dispersed fluorocarbon. Unfortunately, this generally leads to corresponding increases in retention of the FC in the RES. I proposed that the emulsion stability / organ retention dilemma could be overcome by inclusion of small amounts of a lipophilic secondary FC, PFDB. Addition of PFDB also decreased the vapor pressure of the dispersed FC phase leading to decreases in the hyperinflated lung syndrome (HNCL). The HNCL phenomenon was found to be remarkably species dependent, and not considered to be of importance in humans.

Publications and Patents Resulting From This Work:

Weers JG, Johnson C, Klein D: Stabilization of fluorocarbon emulsions. U.S. Patent No. 5,628,930 issued 13 May 97.
Weers JG, Schutt EG, Pelura TJ, Keipert PE: Fluorocarbon emulsions exhibiting reduced pulmonary gas trapping. U.S. Patent No. 5,635,538 issued 3 Jun 97.
Weers JG, Johnson C, Klein D: Methods for the use of stabilization of fluorocarbon emulsions. U.S. Patent No. 5,914,352 issued 22 Jun 99.
Weers JG, Klein DH, Johnson CS: Patient oxygenation using stabilized fluorocarbon emulsions. U.S. Patent No. 6,204,296 issued 20 Mar 01.
Weers JG, Ni Y, Tarara TE, Pelura TJ, Arlauskas RA. The effect of molecular diffusion on initial particle size distributions in phospholipid-stabilized fluorocarbon emulsions. *Colloids Surfaces A: Physicochem Eng Aspects* 1994, 84:81-87.
Schutt E, Barber P, Fields T, Flaim S, Horodniak J, Keipert P, Kinner R, Kornbrust L, Leakakos T, Pelura T, and Weers J: Proposed mechanism of pulmonary gas trapping (PGT) following intravenous perfluorocarbon emulsion administration. *Art Cells Blood Sub Immob Biotech* 1994, 22:1205-1214.
Weers JG, Liu J, Fields T, Resch P, Cavin J, Arlauskas RA: Room temperature stable perfluorocarbon emulsions with acceptable half-lives in the reticuloendothelial system. *Art Cells Blood Sub Immob Biotech* 1994, 22:1175-1182.
Keipert PE, Otto S, Flaim SF, Weers JG, Schutt EA, Pelura TJ, Klein DH, Yaksh TL: Influence of perflubron emulsion particle size on blood half-life and febrile response in rats. *Art Cells Blood Sub Immob Biotech* 1994, 22:1169-1174.
Klein DH, Jones RC, Keipert PE, Luena GA, Otto S, Weers JG: Intravascular behavior of perflubron emulsions. *Colloids Surfaces A: Physicochem Eng Aspects* 1994, 84:89-95.
Weers JG, Harris MB, Otto S, Arlauskas RA: The use of lipophilic secondary fluorocarbons to solve the emulsion stability/organ retention dilemma in blood substitutes. *Art Cells Blood Sub Immob Biotech* 1996, 24:458 (abstract).

Project: *Imagent Reformulation*

Situation: ALLP's ultrasound contrast agent had recently complete Phase I trials, and the agent was found to lead to activation of the complement system
Action Plan: I was asked to lead an effort designed to reformulate the agent without complement activation.
Results: The observed complement activation was traced to a specific component in the formulation. This component was ultimately replaced with a biocompatible phospholipid, and the reformulated product has now received FDA approval.
In the process of conducting the work we also examined in detail the factors controlling the lifetime of microbubble contrast agents in the vasculature. This led to a theoretical treatise and additional patents and publications in the area.

Publications and Patents Resulting From This Work:

Kabalnov A, Klein D, Pelura T, Schutt E, Weers J: Dissolution of multicomponent microbubbles in the bloodstream 1. theory. *Ultrasound Med Biol* 1998, 24:739-749.
Kabalnov, A, Bradley J, Flaim S, Klein D, Pelura T, Peters B, Otto S, Reynolds J, Schutt E, Weers J: Dissolution of multicomponent microbubbles in the bloodstream 2. experiment. *Ultrasound Med Biol* 1998, 24:751-760.
Schutt EG, Evitts DP, Kinner RA, Anderson CD, Weers JG: Stabilized microbubble compositions. U.S. Patent No. 5,639,443 issued 17 Jun 97.
Trevino LA, Schutt EG, Klein DH, Tarara TE, Weers JG, Kabalnov AS: Stabilized gas emulsion containing phospholipid for ultrasound contrast enhancement. U.S. Patent No. 5,798,091, issued 25 Aug 98.
Kabalnov AS, Weers JG, Schutt EG: Gas emulsions stabilized with fluorinated ethers having low Ostwald coefficients. U.S. Patent No. 5,804,162, issued 8 Sep 98.
Kabalnov A, Schutt E, Weers JG: Stabilized gas emulsions containing phospholipids for ultrasound contrast enhancement. U.S. Patent No. 6,193,952 issued 27 Feb 01.
Schutt EG, Evitts DP, Kinner RA, Anderson CD, Weers JG: Osmotically stabilized microbubble preparations. U.S. Patent No. 6,258,339, issued 10 Jul 01
Trevino LA, Schutt EG, Klein DH, Tarara TE, Weers JG, Kabalnov A: Kits and systems for ultrasonic imaging. U.S. Patent No. 6,280,705, issued 28 Aug 01.
Schutt EG, Evitts DP, Kinner RA, Anderson CD, Weers JG: Mixed gas microbubble compositions. U.S. Patent No. 6,372,195, issued 16 Apr 02.

Project: *PulmoSphere Powders for Inhalation*

Situation: Inhale Therapeutic Systems was having difficulty adapting their core particle engineering technology to the delivery of small molecules, and many potential applications were in the small molecule space In addition, their lead PDS device was viewed by many customers as being too large for many applications. To make matters worse, a new competitive porous particle technology was being developed by Advanced Inhalation Research (AIR), with the potential to offer solutions to these issues.
Action Plan: With the completed acquisition of the PulmoSphere technology by Inhale, we were asked to push the technology as rapidly as possible into four Phase I clinical studies to showcase the potential of the technology.
Results: We completed the four Phase I studies in a period of 15 months. The studies demonstrated the remarkable performance of the PulmoSphere technology in the delivery of small molecules and peptides from portable inhalers, including both pressurized metered dose inhalers and passive capsule-based dry powder inhalers. Key results are detailed below.

Drug Substance	Key Result
Albuterol pMDI	Demonstrated that 40% of the ED was deposited in the lung vs. 17% for the Glaxo Ventolin Evohaler
Budesonide DPI	Demonstrated that 67% of the ED was deposited in the lung, independent of th patients PIFR. This was compared to 28% for the commercial Pulmicort Turbuhaler formulation at high PIFR, and 15% at at low PIFR.
Tobramycin DPI	Demonstrated that 25 mg of powder could be tolerably delivered to subjects with high efficiency. Showed that rapid inhalation of three puffs from the DPI could replace 15 minutes on a nebulizer. It is thought that this will lead to improvements in compliance for CF patients.
Leuprolide DPI	Demonstrated that a peptide could be formulated in the PulmoSphere technology, and delivered with high efficiency to the systemic circulation using a passive DPI.

Publications and Patents Resulting From This Work:

Newhouse MT, Hirst PH, Duddu SP, Walter YH, Tarara TE, Clark AR, Weers JG: Efficient and reproducible pulmonary delivery of tobramycin using an engineered PulmoSphere powder. *Chest*, 2003, 124:360-366.
Duddu SP, Sisk SA, Walter YH, Tarara TE, Trimble K, Clark AR, Eldon M, Elton RC, Pickford M, Hirst PH, Newman SP, Weers JG: Improved lung delivery from a passive dry powder inhaler using an engineered PulmoSphere powder. *Pharm Res* 2002, 19:689-695.
Hirst PH, Elton RC, Pitcairn GR, Newman SP, Weers JG, Clark AR, Tarara TE, Dellamary LA, Hall G, Shorr J: In vivo lung deposition of hollow porous particles from a pressurized metered dose inhaler. *Pharm Res* 2002, 19:258-264.
Weers J, Tarara T, Venthoye G: Pulmonary delivery of aminoglycosides. US Serial No 60/342,827, filed 19 Dec 01.
Weers J, Tarara TE: Methods for administering leuprolide by inhalation. US Patent Appl No 2003/0003057 A1, published 2 Jan 03.
Weers J, Tarara T: Methods of tobramycin inhalation. US Patent Appl No 2002/0187106 A1, published 12 Dec 02.